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13. ABSTRACT *(Maximum 200 Words)*

Breast cancer is one of the leading causes of cancer deaths of women in the United States. Fortunately, this disease is no longer a "black box" that can only be studied empirically. Rather, recent advances in understanding of normal mammary development and carcinogenic processes have identified a number of specific genes and processes that are dysregulated in breast cancer. This means that research on breast cancer has finally advanced to the stage where a concentrated effort in translational research will yield great strides in detection, diagnosis, and treatment. The Molecular Medicine graduate training program at Yale was recently developed to address these issues. This program was developed to offer an interdisciplinary course of study that will foster an integrated view of disease, built upon a rigorous foundation of basic sciences. The emphasis on disease mechanisms and translational research is unique to Molecular Medicine, and distinguishes it from other pre-doctoral programs at Yale. The Predoctoral Training Program in Breast Cancer Research will recruit individuals interested in careers in breast cancer research to the Molecular Medicine Program, provide specialist training in breast cancer-specific areas, and integrate their training experience with basic scientists and clinicians investigating breast cancer at Yale.

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(4) INTRODUCTION

The past decade has witnessed a revolution in the power of biologists to investigate fundamental mechanisms underlying disease. This change has resulted from major advances in biological research, coupled with the extraordinary power of modern molecular genetics for identification of gene mutations in disease. The result is that investigation of many human diseases has gone beyond the descriptive level to the root causes. This new knowledge means that the tools of genetics, immunology, cell biology, molecular biology, and other disciplines can now be combined to investigate disease pathogenesis, and to apply these findings to issues of diagnosis and treatment. The Molecular Medicine graduate training program at Yale was recently developed to address these issues. This program was developed to offer an interdisciplinary course of study that will foster an integrated view of disease, built upon a rigorous foundation of basic sciences. The emphasis on disease mechanisms and translational research is unique to Molecular Medicine, and distinguishes it from other pre-doctoral programs at Yale. The Predoctoral Training Program in Breast Cancer Research will recruit individuals interested in careers in breast cancer research to the Molecular Medicine Program, provide specialist training in breast cancer-specific areas, and integrate their training experience with basic scientists and clinicians investigating breast cancer at Yale.

(5) BODY

We are now completing the first year of this new training program.

Recruitment. Class entering Fall 1999. As discussed in the proposal, trainees are recruited through the Pharmacological Sciences and Molecular Medicine Program of the university-wide combined BBS training program. The award for this grant was activated in summer, 1999 to fund students entering the Program in Fall, 1999. Because of the timing of the USAMRMC grant program relative to the academic year, students funded during year 1 of the grant had been admitted prior to approval of the grant. These students had been admitted the previous Spring. A description of the applicant and admitted pool is provided in Table 1. Students chosen for funding by the program in the first year were those whom we felt were most likely to remain in cancer research from the entering class.

Class entering Fall, 2000. In order to enhance recruitment for the program, we assembled a poster and a Web site (http://info.med.yale.edu/pathol/bcr/index.html) as adjuncts to the BBS recruiting information. A copy of the poster is provided in the Appendix. This poster was distributed by mail to over 3500 academic units including programs in Biological and Biomedical Sciences, Developmental Biology, Experimental Biology, Genetics, and other relevant disciplines.

Training. The first year in graduate school consists of course work and a series of research rotations. All incoming students were oriented along with other students in the Pharmacological Sciences and Molecular Medicine Track, and assigned to trainers and Track Directors William Sessa and David Stern as advisors. The advisors met with the students to jointly plan out a curriculum for the first year. In year 1, this consists of course work and three laboratory rotations. The rotations serve to train individuals in design, execution, and interpretation of laboratory research projects, to expose the trainees to a variety of research experiences, and to enable trainees to identify compatible

dissertation advisors. Students are required to choose a dissertation advisor the end of the first year.

Course work. As discussed in the proposal, the purpose of coursework is to ensure that students have a strong basic science foundation that complements undergraduate coursework, and to provide students with advanced and specialty knowledge. This process will continue in year 2, with inclusion of breast-cancer-specific training. Classes taken by the first year students are described in Table 3, and include "foundation" courses such as cell biology and genetics, and more specialized coursework in cancer and disease mechanisms.

Year 1, rotations. The rotation advisors and rotation topics for year one are shown in Table 2. Four of the 15 rotations were done in labs of trainers, and each student except KPK rotated in at least two trainers' labs. (KPK did settle in a trainer lab.)

A description of rotation projects follows.

Kian Peng Koh.

Barbara Ehrlich
Localization of the low-affinity IP3 binding site on the IP3 receptor.
Yung Chi Cheng
Characterization of the phosphotransferase reaction intermediates of the nucleoside-diphosphate kinases Nm23-H1 and Nm23-H2.
Jordan Pober
Characterization of the anti-apoptotic pathways activated by the TNF/PI3-kinase/Akt pathway in endothelial cells.

Soo Jung Lee.

David Stern
Rad53 binding proteins induced by the DNA replication checkpoint
Willam Sessa
Cellular localization of phosphorylated endothelial nitric oxide synthase
Michael Snyder
Analysis of protein kinases using protein microarrays.

Jessica Hawes.

Archibald Perkins
Protocol Refinement/Development of a cDNA microarray assay for comparison of cancerous and non-cancerous tissues.
David Rimm
Search for proteins that preferentially bind tyrosine-phosphorylated beta-catenin, which may be involved in the differential regulation of beta-catenin between its roles in cell-cell adhesion and regulation of the TCF/LEF transcription complex.
Joseph Madri
Examined the cellular localization of MMP 2, MT1-MMP, and TIMP 2 at sites of invadopodia during angiogenesis.
Craig Crews
Investigated Methionine Aminopeptidase 2 activity as a necessary factor in myristoylation of c-Abl and subsequent stabilization/activation of p53

Julie Wu.

Lucia Languino.
Beta1a and Beta1c integrin regulation of focal adhesion kinase
David Stern
Search for mutations in the candidate tumor suppressor gene CHK2 in breast cancer tissue
Anton Bennett.
SHP-2 regulation of p38 MAPK.

Selection of dissertation advisers. Since, under the BBS program, students are free to rotate throughout the university, it was inevitable that there would be some attrition between years one and two. Of the three students funded in year one of the program, two (KPK and SL) affiliated with program trainers. A third (MG) affiliated with Dr. Henrik Dohlman, an expert on G-protein coupled receptors. In deciding whether these students would be reappointed to the program in year 2, we took into account, not only the adviser, but the relatedness of the dissertation project to breast cancer. On this basis, we retained Soo-Jung Lee in the program. Mr. Koh will be working in trainer Pober's laboratory, but in an area only distantly related to cancer. Ms. Granovskaya will work on sorting of caveolar proteins using a yeast system. Since caveolae are implicated as depots for a number of important growth regulatory signaling proteins, the project has strong cancer relevance, but Dr. Dohlmann is not one of our trainers.

In year 2 these students will complete coursework, including breast cancer training, qualifying exams, and will begin to lay the foundation for the dissertation. Although the students have dissertation advisors, the dissertation project is not formalized until the prospectus exam, which must be completed by the end of year 3. A brief description of research directions of the five students is now provided, with the caveat that it may be some time before the projects fully evolve.

Trainees and their projects.

Marina Granovskaya (no longer funded by training program). Ms. Granovskaya is not presently funded by this program because her dissertation adviser, Henrik Dohlman, is not a trainer on this grant. Marina Granovskaya's current project is to (1) reconstitute caveolae formation in yeast S. cerevisiae (an organism that lacks caveolin or caveolae), (2) determine the functional consequences of caveolae formation for G protein signaling in yeast, (3) isolate G protein mutants that fail to assemble into caveolae, and (4) determine the functional consequences for analogous G protein mutants in mammalian cells.

Breast cancer relevance. Caveolae are thought to function as functional domains within the plasma membrane where specific subsets of signaling proteins gather. Several proteins important to breast cancer have been localized to caveolae, including oncogenes HER2/neu and Src. Shuttling in and out of caveolar compartments is thought to regulate interactions of intramembrane signaling molecules.

Kian Peng Koh (no longer funded by training program). Mr. Koh is in the laboratory of trainer Jordan Pober. However, since he is working on the cardiovascular system, his work falls outside the scope of the training grant, so he is being funded through other resources. His subject is the mechanism of endothelial dysfunction in the pathogenesis of transplantation-associated arteriosclerosis. The immediate goal is to assess the possibility of performing vascular functional assays on arteries cultured for 1-2 weeks on a collagen gel system. If

feasible, the system will provide a novel in vitro/ex vivo approach to study whether leukocytes, cytokines or the combination of factors induces endothelial dysfunction in transplanted vessels.
Breast cancer relevance is limited, although the process angiogenesis is important in carcinogenesis.

Soo-Jung Lee. Ms. Lee is working in the laboratory of the program director, Dr. Stern. The major components of DNA checkpoint pathways have been shown to be conserved between budding yeast and humans. The Stern lab is investigating DNA checkpoint pathways connecting DNA damage to activation of the yeast ortholog of human Atm (yeast Mec1), which in turn activates human Chk2 (yeast Rad53). Work in Dr. Stern's lab has developed an explicit model for the mechanism, which involves an intermediary protein possibly homologous to Brca1 (budding yeast Rad9) interacting via a phospho-peptide recognition domain on Rad53. Ms. Lee is determining how complexes containing yeast proteins homologous to human Hus1, Rad1, and Rad9 (unrelated to yeast Rad9) regulate this pathway.

Breast cancer relevance. This work is directly relevant to breast cancer, since it is now clear that Chk2 is an intermediary linking DNA checkpoint pathways from candidate breast cancer tumor suppressor Atm to breast cancer tumor suppressor p53; since Chk2 phosphorylates and modulates Brca1 function, and since Chk2 mutations are found in variant p53+ forms of Li-Fraumeni syndrome, which predisposes to breast cancer and other cancers.

Julie Wu. Ms. Wu is working in the laboratory of trainer Anton Bennett. Mitogen activated protein kinase (MAP) phosphatase 1 (MKP1) is a dual specificity tyrosine/threonine phosphatase that is highly regulated by growth regulators and stress. It dephosphorylates MAPK family members. MKP1 regulates the activities of p38 (Stress activated protein kinase) and ERKs. Attenuation of MAPK activity after activation is a tightly regulated process.

The four isoforms of p38 are each encoded by distinct genes. They response to different stimuli and they differntially regualte biological functions including apoptosis, proiferation and differentiation. Ms. Wu will examine MKP1 regulation of p38 in the liver during the stress response, and will also evaluate p38 activity in MKP1 knockout mice.
Breast cancer relevance. MAPKs are major regulators of cell growth and apoptosis. Oncogenes such as Ras and ErbB2 function in part through activation of MAPKs. Regulation of MAPK attenuation may be as important as regulation of activation. Inability to attenuate the activity of activated proteins results in abnormal biological processes. Inability to attenuate a p38 MAPK activity during stress may uncouple the cell's ability to respond to stress and repair induced damage. This may result in gene mutations, and/or unregulated growth, two hallmarks of cancer.

Table 1. Applicant pool. Class entering 1999-2000.

INSTITUTION	DEGREE	YEAR	GPA	V	Q	A	admitted	enrolled
Pitzer College	BA	1998	3.65	560	680	750	Y	Y
Mass Institute of Technology	BS	1999	3.60	690	710	750	Y	Y
Connecticut, Univ of--Storrs	BA	1996	2.56	570	690	780	Y	Y
Moscow State University	BS/MS	1999		330	610	690	Y	Y
Weber State University	BS	1999	3.57	440	740	750	Y	Y
Williams College	BA	1999	3.95	650	780	730	Y	Y
Yale University	BS	1995		490	740	580	Y	Y
Seoul National University	BS	1994	3.15	550, 660	760, 770	620, 670	Y	Y
Hollins College	BA	1997	3.95	650	560	710	Y	Y
Florida State University	BS	1994		630	580	750	Y	Y
SUNY At Stony Brook	BS	1999	3.60	410	630	620	Y	Y
Swarthmore College	BA	1998		710	690	750	Y	
Cornell University	BA	1999	4.00	620	800	580	Y	
Calif, Univ of-Davis	BS	1998	3.69	600, 690	780, 800	660, 690	Y	
SUNY At Stony Brook	BS	1997	3.64	730	710	660	Y	
Rutgers Univ--New Brunswick	BA	1994	3.22	570, 610	650, 720	640, 780	Y	
Lycoming College	BS	1998		750	800	760	Y	
Univ of Maryland-CollegePark	BS	1999		760	780	800	Y	
Yale University	BS	1999		670	750	690	Y	
Cornell University	BA	1995	3.74	760	720	710	Y	
Michigan, Univ of--Ann Arbor	BS	1997	3.83	660	790	790	Y	
Central Michigan University	BS	1999	3.98	650	740	760	Y	
Wisconsin, Univ of--Madison	BS	1997	3.37	500, 510	640, 650	620, 750	Y	
Willamette University	BA	1999	3.02	510	700	770	Y	
Arizona, University of	BS	1999					Y	
London, University of	BS	1999		630	740	670		
Humboldt State University	BS	1999	3.74	460	580	620		
Carnegie Mellon University	BS			440	730	800		
Albany College of Pharmacy	BS	1999	3.60	490	590	600		
Harvard-Radcliffe College	BA	1999		750	750	710		
Johns Hopkins University	MPH	1994		620, 690	670, 720	590, 610		
National Yang Ming University	MD	1995		570	790	650		
Other Institution	BS	1993		570	770	630		
Virginia, University of	BS	1997	3.03	540	700	680		
Shanghai Medical University	BS	1998		540	780	760		
Other Institution	MS	1995		660	790	710		
American Univ Beirut	BS	1995	2.96	450	680	660		
Shanghai Medical University	BS	1996		670	790	700		

George Mason University	BS	1998	3.75	540	590	630		
Wesleyan University (Conn)	BA	1998		520, 540	550, 680	530, 570		
Calgary, University of	BS	1999	3.35	570	770	750		
Northeastern University	MS	1999		500	750	740		
Other Institution	BS	1993		520	710	580		
Pace University--Pleasantvill	BS	1999	4.00	570	680	620		
Howard University	BS	1998	3.16	320, 380	400, 410	360, 390		
Hebrew University	DVM	1992		530	670	560		
Yale University	BA	1997	3.30	670, 700	620, 660	670, 680		
William & Mary, College of	BS	1999	2.87	600	710	650		
Earlham College	BA	1999	3.66	500	720	700		
National Taiwan University	MD	1997		550	800	710		
Nebraska, Univ of--Lincoln	BS	1999	3.96	630	680	800		
Calif, Univ of-Berkeley	BA	1998	3.52	580	750	610		
McMaster University	BS	1998		720	740	780		
Pittsburgh,Univ of--Pittsburg	BS	1999	3.91	450, 460	710, 740	480, 500		
London, University of	BS	1999		510	640	640		
New Mexico State U--Las Cruce	BS	1997	3.91	400, 420	490, 600	560, 700		
Imperial College	BS	1999		590	720	560		
Rochester, University of	MS	1995		460	610	500		
Calif, Univ of-Berkeley	BS	1998	3.31	630	620	550		
Other Institution	MD	1999	3.59	710	790	730		
Other Institution	BS	1996		650	760	700		
Hampshire College	BA	1999		650	720	630		
Other Institution	MD	1998						
Tufts University	DVM	1993		460	670	540		
Dartmouth College	BA	1998	3.21	660	720	710		
Wooster, College of	BA	1999	3.63	490	680	580		
Centre College (Kentucky)	BS	1999	3.31	570	690	570		
McGill University	BS	1997	3.48	480	710	670		
Fudan University	BS	1999		640	800	670		
Oklahoma State University	MS	1991		500	780	670		
Other Institution	MD	1998		590	780	720		
Other Institution	BS	1999	3.95	480	800	800		
Calif, Univ of-Berkeley	BA	1998	3.65	490, 580	770	660, 710		
Trinity University (Texas)	BS	1999	3.21	640	620	730		
Oklahoma, University of	BS	1998	3.68	560	750	690		
Gannon University	BS	1995	3.05					

Calif, Univ of-Berkeley	BS	1999	3.67					
Tokyo, University of	BE	1999						
Rochester Inst of Technology	BS	1999	3.89					
Bennett College	BS	1999	3.92					
Nankai University	BS	1997						
SUNY At Stony Brook	BS	1999	3.32					
National Taiwan University	BS	1996						
Beijing University	BS	1999						
Beijing University	BS	1999						

Table 2. Students and rotations.

	students entering Fall, 1999 Student	**Rotations and Dissertation Advisors** ***= BCRTP trainer**	**students entering Fall, 2000**
Year 1 1999-2000	Marina Granovskaya Soo-Jung Lee Kian Peng Koh	Perkins*, Languino*, Dohlmann Stern*, Sessa*, Snyder Ehrlich, Pober*, Cheng	
Year 2 2000-2001	Jessica Hawes Soo-Jung Lee Julie Wu	Perkins*, Crews*, Madri* Stern*, Sessa*, Snyder Languino*, Bennett*, Stern*	Seda Eminaga Kristen Massimine Alexander Urban

Table 3. Coursework by trainees, year 1.

	Granov -skaya	Hawes	Lee	Koh	Wu
Fall term.					
Cell Biology 602a Molecular Cell Biology		•	•	•	•
Genetics 625a Basic Concepts of Genetic Analysis		•	•	•	
Pathology 680a seminar Topics in Molecular Medicine: Matrix Biology	•	•	•	•	•
Pharmacology I:Maintaining and restoring homeostasis	•				•
Pathology 640a From Molecular Biology to Molecular Medicine	•				
MBandB 752a Genomics/Bioinformatics	•				
Spring term.					
Pathology 650b Cellular and Molecular Biology of Cancer	•	•	•		•
Pathology 690b Mechanisms of Disease		•		•	
Pharmacology II: Interfering selectively	•	•	•	•	•
Pharm 502b seminar	•	•	•	•	•

(7)Accomplishments

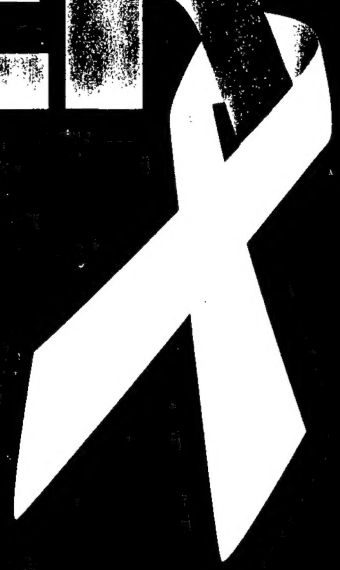
- Recruitment of a highly qualified group of students interested in cancer research.
- Guiding students through an appropriate series of classes, including training in cell biology, disease mechanisms, cancer, and pharmacology.
- Providing students with research rotations relevant to cancer research.
- Selection of second year students with dissertation projects relevant to breast cancer research for further training through the program.

Reportable outcomes.

None.

breast CANCER

Research Training Program at Yale University



the program:

Breast cancer is one of the leading cancer killers of women. Thanks to recent scientific advances, this disease is finally beginning to yield ground. The Training Program in Breast Cancer Research offers an interdisciplinary course of studies leading to the

the training:

The program fosters an integrated view of disease, built upon a rigorous foundation of basic sciences including cell biology, molecular genetics, and

the faculty:

David F. Stern, PhD, Director
Dario C. Altieri, MD,PhD
Karen S. Anderson, PhD
Anton. M. Bennett, PhD

leading cancer killers of women. Thanks to recent scientific advances, this disease is finally beginning to yield ground. The Training Program in Breast Cancer Research offers an interdisciplinary course of studies leading to the Ph.D. Unique features of this program are the emphasis on disease mechanisms, and translation to the clinic, as well as the specific focus on breast cancer. Areas of dissertation research include signal transduction, cell cycle regulation, apoptosis, mammary development, cancer genetics, and pharmacology.

the training:

The program fosters an integrated view of disease, built upon a rigorous foundation of basic sciences including cell biology, molecular genetics, and pathogenesis. Students acquire a firm foundation in basic sciences through course work and seminars. Students gain specialty training in breast cancer through joint activities with the Yale Comprehensive Cancer Center. The training program is a component of the university-wide combined program in Biomedical and Biological Sciences (BBS).

the faculty:

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Nancy Berliner, MD
Jose Costa, MD
Craig Crews, PhD
Pietro DeCamilli, MD
Michael DiGiovanna, MD,PhD
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Lucia Languino, PhD
Richard Lifton, MD,PhD
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Vincent Marchesi, MD,PhD
Jon Morrow, MD,PhD
Archibald Perkins, MD,PhD
Jordan Pober, MD,PhD
Michael Reiss, MD
David Rimm, MD,PhD
William Sessa, MD,PhD
Mark Solomon, PhD
Hong Sun, PhD
Barbara Ward, MD

For more information:

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Michael Reiss, MD
David Rimm, MD,PhD
William Sessa, MD,PhD
Mark Solomon, PhD
Hong Sun, PhD
Barbara Ward, MD
Trevor Williams, PhD
John Wysolmerski, MD
Hui Zhang, PhD

(3)

students may elect to train with other BBS faculty at Yale

For more information:

http://info.med.yale.edu/pathol/bcr

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